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Attempted Preparation of 1-Diazo-6-Methoxy-2-Hexanone

Edmund Joseph Zalewski
Union College - Schenectady, NY

ATTEMPTED PREPARATION OF
1-DIAZO-6-METHOXY-2-HEXANONE

by

Edmund Joseph Zalewski III

Senior Thesis Submitted

in Partial Fulfillment

of the Requirements of Graduation

DEPARTMENT OF CHEMISTRY

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This Thesis

Submitted by

Edmund Joseph Zalewski

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is approved by

Howard E. Sheffer

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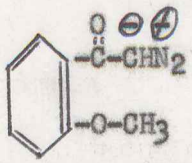
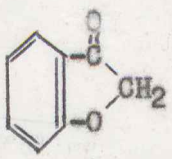
ILLUSTRATIONS

HISTORICAL

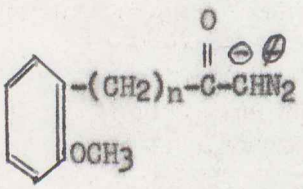
Diazoketones were discovered by L. Wolff[1] whose studies led to the process of transforming diazoketones in the presence of silver ions to carboxylic acids. Later discoveries by Arndt and Eistert[1] showed that carboxylic acid chlorides treated with a cold solution of diazomethane in ether could be transformed into diazoketones.

Later work by Rose and Yates[2] showed that ∝-diazo-o-methoxyacetophenone (I) could be converted to coumaranone (II) when treated with a mineral acid.

(I) 

(II) 

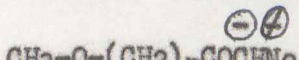
Sheffer and Moore [3] found that a Lewis acid such as boron trifluoride can be used on o-methoxy aromatic diazoketones (III)

(III) 

where: n = 0 or 1

to yield cyclic products, but undesireable side reactions occur which yield fluoro, hydroxy and ethoxy substituted methyl ketones.

Hoster, D. P.[4] and Thielking, W. H. [5] attempted to adapt the work done by Sheffer and Moore to aliphatic compounds, having the general structure



where: n = 1, 2 or 3

Their work showed no appreciable yield of cyclic compounds upon treating the methoxydiazoketones with boron trifluoride etherate.

APPARATUS:

For the purpose of removing solvent or for the purification of the δ-valerolactone distillation was carried out using an eighteen inch, six-ball Snyder distilling column. Quantitative separations were performed using a F & M Scientific Corp., Model 720 Gas-Chromatograph equipped with either a six-foot or nine-foot column. Both columns were identical, in that each was packed with substrate coated with Celanese Ester #9.

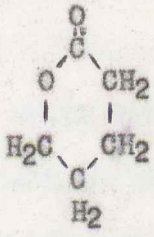
To determine functional groups and to characterize materials, a Perkin-Elmer Infracord spectrophotometer was used. The optics used in all cases were sodium chloride.

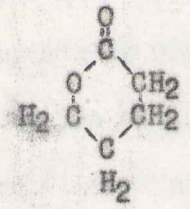
An Abbe Refractometer was used as an aid in characterizing materials which had been previously reported in literature.

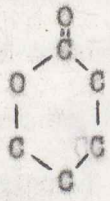
Other apparatus used consisted of those found in any laboratory stockroom, such as, flasks (3 and 4 neck), water cooled condensers, manometer (Bennert type), Erlenmeyer flasks, magnetic stirrers (equipped with Teflon coated magnet), and vacuum pump.

Proposed Scheme

For Obtaining 1-Diazo-6-Methoxy-2-Hexanone

(1) $HO-(CH_2)_5-OH \xrightarrow{Cr_2O_3 \cdot 2CuO}$ 

(2)  $+ NaOCH_3 \xrightarrow{CH_3OH}$ $CH_3-O-(CH_2)_4-C(=O)-OH + HO-(CH_2)_4-C(=O)-O-CH_3$

(2a)  $+ NaOCH_3 \longrightarrow CH_3-O-(CH_2)_4-C(=O)-ONa + NaO-(CH_2)_4-C(=O)-OCH_3$

(3) $CH_3-O-(CH_2)_4-C(=O)-ONa + CH_3I \longrightarrow CH_3-O-(CH_2)_4-C(=O)-OCH_3$

(3a) $NaO-(CH_2)_4-C(=O)-OCH_3 + CH_3I \longrightarrow CH_3-O-(CH_2)_4-C(=O)-OCH_3$

(4) $CH_3-O-(CH_2)_4-C(=O)-OCH_3 + NaOH \longrightarrow CH_3-O-(CH_2)_4-C(=O)-ONa$

(5) $CH_3-O-(CH_2)_4-C(=O)-ONa \xrightarrow{H^+} CH_3-O-(CH_2)_4-C(=O)-OH$

(6) $CH_3-O-(CH_2)_4-C(=O)-OH \xrightarrow{SOCl_2} CH_3-O-(CH_2)_4-C(=O)-Cl$

(7) $CH_3-O-(CH_2)_4-C(=O)-Cl + \overset{\ominus}{C}H_2 \overset{\oplus}{N}_2 \longrightarrow CH_3-O-(CH_2)_4-C(=O)-\overset{\ominus}{C}H \overset{\oplus}{N}_2$

The synthesis of δ-methoxyvaleric acid

$CH_3-O-CH_2-CH_2-CH_2-CH_2-COOH$

and methyl δ-methoxyvalerate

$CH_3-O-CH_2-CH_2-CH_2-CH_2-COOCH_3$

was carried out by Palomaa and Kenetti[6] in their study of the reaction kinetics of methoxyvaleric acid with various hydroxyl bearing compounds. The acid was obtained through the malonic ester synthesis. The yield of the δ-methoxyvaleric acid based on the starting component was in the neighborhood of 35%. This same method was used later by Leimu[7] with approximately the same yield based on the starting component.

Since δ-valerolactone had already been made by Schniepp and Geller[8] using an oxidation process, in good yields and simple procedure, it was thought that the δ-methoxyvaleric acid could be arrived at using a technique developed by Bartlett and Rylander[9] to synthesis β-methoxypropionic acid. β-Methoxypropionic acid was obtained in good yields by Bartlett and Rylander from the reaction of β-propiolactone and methyl alcohol containing a catalytic amount of sodium methoxide.

EXPERIMENTAL

Preparation of δ-valuolactone Reaction R-1

To a 3-liter, 4-neck flask equipped with agitator, two condensers in series and a thermometer was added 416g. (4 moles) distilled 1,5-pentanediol (Carbide and Carbon Chemicals Co.) along with 12 g. (0.039 mole) copper chromite catalyst (Union College Chemistry Dept.).(10) The mixture was thoroughly mixed and heated under reflux. When the temperature reached 210°, a vigorous evolution of hydrogen began. The reaction was continued for an additional 45 minutes, at which time the temperature had risen to 245° and the evolution of gas had slowed down considerably. The apparatus was then converted from one of reflux to that of vacuum distillation and the reaction mixture subjected to vacuum distillation. The distillate was found to weight 351 g.

The first attempts using this method, were made on a much smaller scale, 52 g. (0.5 mole) 1,5-pentanediol. Caution was exercised because of the large quantity of hydrogen evolved from the reaction (approx. 22 l.). These small quantities of reaction product were being accumulated, so that the final purification could be done on a large scale. After a period of 5 weeks, it was noticed that the reaction products were becoming cloudy. Upon examination of all the samples, it was observed that the turbidity in the first reaction was the greatest with a gradual decrease to reaction 10. This, beacuse it was only two weeks old, was only slightly turbid. Reactions 11 through 15 has not yet been affected as all reactions were stored at 5°. A deeper search into the

literature revealed that δ-valerolactone begins to polymerize with itself in 50 hrs. at room temperature and that the resulting polymer is not compatible with the lactone[11].

Reaction product R-1 was found to contain 90.2% δ-valerolatone by separation using gas-chromatograph techniques. Better purification was achieved by addition of phenyl isocyanate (Mobay Chemical Co.) to yield a percipitate of the bis-phenylurethane of 1,5-pentanediol.

Purification of -valerolactone Reaction R-2

Reaction product R-1 (203 g.) was added to a 500 ml. Erlenmeyer flask containing 63.3 g. (0.53 mole) phenyl isocyanate. The mixture was shaken and then allowed to stand for thirty minutes at room temperature, after which time, one ml. of water was added to react any unreacted phenyl isocyanate. The major portion of the bis-phenylurethane of 1,5-pentanediol was removed by filtration, and the liquid was subjected to vacuum distillation. The distillate yield was found to be 179.8 g. with the following properties:- b.p. 104° (10 mm. Hg), n_d^{25} 1.4568.

The reported values were 105° (8 mm. Hg) and n_d^{25} 1.4553[8]. Gas-chromatograph analysis showed that 99.3% δ-valerolatone had been obtained and an aqueous titration using phenolphthalein indicator and 0.1 N KOH yielded a neutralization equivalent of 99.6[12]. An infrared spectrum was run on the lactone (Spectrun #2) and the absorption bands conformed to those expected, especially the band at 1740 cm-1 which is reported to be the characteristic absorption for δ-valerolactone[13].

Preparation of Methyl δ-methoxyvalerate and δ-methoxyvaleric Acid

Reaction R-3

To a 250 ml. Erlenmeyer flask containing 5 g. (0.05 mole) δ-valerolactone (R-2) was added 2.7 g. (0.05 mole) sodium methoxide (Fisher Scientific Co.). The mixture was stirred and allowed to stand 24 hrs. at room temperature. The flask was equipped with a rubber stopper, to exclude any moisture from the air.

At the end of the 24 hr. period, the product, a yellowish-waxy paste, was dissolved in water warming the ingredients slightly to facilitate salvation of the waxy material. The solution was then acidified with dilute hydrochloric acid to a pH less than six. The solution was then extracted with 1-butanol and the extracted portion dried with anhydrous sodium sulfate (Fisher Scientific Co.). At the end of a thirty minute period, the sodium sulfate was removed by filtration and the filtrate transferred to a distillation flask. The 200 ml. distillation flask was equipped with an eighteen-inch, six-ball Snyder distillation column and water-cooled condenser. The 1-butanol was then distilled at a pressure of 10 mm. Hg, in order that the temperature could be kept as low as possible to minimize any effects heat might have on the reaction products. The residue remaining after distillation contained a slurry of liquid and what appeared to be salt. The contents of the distillation flask were transferred to a test tube and centrifuged. The decanted liquid was amber in color and was found to weigh 4.9 g., which would be 74.3% of the theoretical yield. Analysis by gas-chromatograph showed

two major ingredients, besides butanol which having been trapped, were characterized by Infra-red analysis. The major peak being identified as δ-valerolactone (Plate #5) and the minor peak which was never identified in Plate #6. Plate #5 was identified as δ-valerolactone, by comparison with an authentic sample.

Reaction R-4

Sodium methoxide, 2.7 g. (0.05 mole), was added to a 250 ml. Erlenmeyer flask containing 5 g. (0.05 mole) δ-valerolactone and the flask sealed with a rubber stopper. The contents of the flask were swirled and then allowed to stand at room temperature for thirty minutes. At the end of this time, 7.1 g. (0.05 mole) methyl iodide (Eastman Organic Chemicals) were added and the flask fitted with a condenser and placed on a hot plate which had a surface temperature of 90°. The flask remained on the hot plate for a period of two hours, after which time it was removed and the contents removed by dissolving them in 1-butanol. The 1-butanol was removed using the same distillation procedure used in R-3 and followed by centrifuging. The liquid weighing 5.2 g. (78.8% of theoretical) was analyzed on the gas-chromatograph as 0.5% methyl δ-methoxyvalerate (Plate #3), 55.5% δ-valerolactone and 44% 1-butanol. (See run R-10 for identification of methyl δ-methoxyvalerate.)

Reaction R-5

Methyl alcohol, 100 ml. (Fisher Scientific Co.), was added to a 250 ml. Erlenmeyer to which also was added sodium methoxide, 2.7 g. (0.05 mole).

The contents of the flask were mixed, and then δ-valerolactone, 5 g. (0.05 mole), was added. The contents were then stirred and allowed to stand 24 hours at room temperature. At the end of this period, the excess methyl alcohol was vacuum distilled and the remaining contents neutralized with dilute hydrochloric acid to a pH of less than six. The aqueous solution was extracted with 1-butanol and dried with sodium sulfate. The distillation and centrifuging procedures used in R-3 were then followed, resulting in 3 g. of liquid (45.4% of theoretical). Analysis showed the sample contained 7.7% δ-valerolactone and 92.3% material identical to Plate #6.

Reaction R-6

Reaction R-6 is essentially the same as R-5 except that the conditions of reaction were changed. Before the δ-valerolactone was added, the mixture of sodium methoxide and methyl alcohol were cooled in a dry ice-acetone bath. After all ingredients were mixed thoroughly, the reaction mixture was allowed to remain in the bath for a period of twelve hours. At the end of this period, the flask was removed from the bath and allowed to come to room temperature. The reaction mixture was neutralized with dilute hydrochloric acid, with an excess added to bring the pH below six. Extraction with toluene (Fisher Scientific Co.) was tried and it was found that 100 ml. of toluene extracted 0.5 g. of material. The remainder of the material was extracted with 1-butanol and separated by vacuum distillation. Yield of liquid was 2.3 g., which is

not a true yield, as much of the material was probably lost in the investigation of various extraction materials. Analysis by gas-chromatograph and Infra-red disclosed approximately 11% methyl σ-methoxyvalerate and 89% σ-valerolactone.

Reaction R-7

To a 250 ml. Erlenmeyer flask containing 100 ml. toluene was added sodium methoxide, 2.7g. (0.05 mole). The mixture was stirred. σ-Valerolactone, 5 g. (0.05 mole) was added with continued agitation. The flask was stoppered and allowed to remain at room temperature for twelve hours, after which time the mixture was neutralized with dilute hydrochloric acid to a pH of less than six. The mixture was then extracted with 1-butanol and separated to yield a liquid weighing 2 g. (30.3% of theoretical), 61.3% of the material being identical to Plate #6 and 38.7% σ-valerolactone.

Reaction R-8

Same as Reaction R-7, except that toluene and sodium methoxide were cooled in a dry ice-acetone bath previous to the addition of σ-valerolactone. Reaction mixture remained in the dry ice-acetone bath for a period of twelve hours, after which time the mixture was neutralized with dilute hydrochloric acid to a pH of less than six. The mixture was extracted with toluene to yield a liquid, amber-colored sample weighing 1.8 g. which was a very poor yield (27.3% theoretical). Upon analysis using the gas-chromatograph and Infra-red it was found that the sample contained 95% σ-valerolactone.

Reaction R-9

To a 500 ml. Erlenmeyer flask containing 235 ml. toluene, was added sodium methoxide, 27 g. (0.5 mole), with constant agitation using a magnetic stirrer 50 g. (0.5 mole) δ-valerolactone was added. A slight exotherm was noted, as the temperature rose from 25° to 38°. The reaction mixture was allowed to agitate for one hour, after which time an orange-colored, pasty, semi-solid type material precipitated from the toluene. At this point, 71 g. (0.5 mole) methyl iodide were added and the reaction allowed to agitate for an additional hour. At the end of this period, the toluene appeared an amber color with a white precipitate, which is believed to be sodium iodide. The solution was filtered and the toluene removed using vacuum distillation. The sample which was amber colored weighed 13.5 g. and was found to contain 82% δ-valerolactone and 18% methyl δ-methoxyvalerate.

Reaction R-10

Similar to Reaction R-9, except that the additions were all made while cooling with dry ice-acetone. At the end of one hour time, the mixture containing sodium methoxide and δ-valerolactone in toluene was still cloudy, so the reaction was allowed to come to room temperature and then agitated for an additional half hour. The orange-gelatinous precipitate which had been observed previously appeared after fifteen minutes had passed. At the end of this time, 71 g. (0.5 mole) methyl iodide were added and the reaction carried out using continuous agitation for a period of one hour at 90°. The toluene was removed by vacuum distillation, and

the product continued to be heated at a pressure of 8 mm Hg. Fractions were taken at 5° intervals starting at 82° and continuing to 107°. The total weight of the fractions totaled 32.65 g. and 6.4 g. of a tar-like material remained in the distillation flask. The first fraction, taken at 82° displayed four peaks using gas-chromatographic techniques, the first of which is methyl δ-methoxyvalerate #3. The second, third and fourth peaks were identical to spectra shown on Plates #4, #5 and #6, with the materials being present in amounts of 58.3%, 8.3%, 16.7% and 16.7% respectively. In all subsequent fractions, the first peak (methyl δ-methoxyvalerate) had disappeared, but the other components were found in different proportions.

The first fraction was run repeatedly through the gas-chromatograph, trapping the material corresponding to the first peak. Approximately, 0.5 g. of this material were accumulated and a micro-boiling point of 184.5° was observed, which corresponds with the reported value for methyl δ-methoxyvalerate of b.p. 184.5-185.5°(6). The index of refraction was also determined n_d^{25} 1.4138, although no value was given in the literature for comparison. Saponification equivalent was 312 (calculated value for methyl ester - 384 and for butyl ester - 298).

The major product was recovered lactone. Minor portions of methyl δ-methoxyvalerate were obtained. The unknown material corresponding to Plate #6 was obtained in significant quantity. Ten per cent of tar was obtained in this reaction.

REACTION SUMMARY

RE-ACTION	SOLVENT	$NaOCH_3$ TEMP. °C.	MeI	MeI TEMP. °C.	RECOVERED δ-LACTONE	METHYL δ METHOXY VALERATE	BUTYL δ METHOXY VALERATE	PLATE #6
* R-3	None	25	---	---	Major	---	---	Minor
R-4	None	25	Yes	25	99	1.0	---	---
* R-5	Methanol	25	---	---	8	---	---	92
* R-6	Methanol	-70	---	---	89	11	---	---
* R-7	Toluene	25	---	---	39	---	---	61
* R-8	Toluene	-70	---	---	95	---	---	---
R-9	Toluene	25	Yes	90	82	18	---	---
R-10	Toluene	-70	Yes	90	Peak #3 Major	Peak #1 Minor	Peak #2 Minor	Peak #4 Inter-mediate

* Neutralized HCl to pH 6

DISCUSSION

The synthesis of methyl δ-methoxyvalerate was accomplished in 20% yield.

The experimental evidence from product analysis alone seems to indicate that sodium methoxide reacts with δ-valerolactone by carbonyl addition almost exclusively rather than by SN_2 displacement. There is one possible exception to this statement and that is the low temperature run, R-6 with sodium methoxide in methanol. The carbonyl addition mechanism would yield as the product the sodium salt of methyl δ-hydroxyvalerate, which on neutralization would yield methyl δ-hydroxyvalerate (Fig. 1).

The high recovery of δ-valerolactone obtained in reactions R-3, R-4, R-6, R-8 and R-9 might be due to hydrolysis of the ester under the acidic conditions of product isolation to the hydroxy acid which would readily form the lactone (Fig. 1). The appearance of the lactone in the final product cannot be due entirely to unreacted lactone, as treatment of the lactone with sodium methoxide ought to be severe enough to open the lactone ring. This conclusion is strengthened by the fact that an orange-reaction product resulted when sodium methoxide was added to the lactone.

The reaction sequence, lactone-sodium methoxide-methyl iodide, resulted in the formation of methyl δ-methoxyvalerate in 20% yield in R-6 and R-9, but only in very small amounts in R-4 because of the lower temperature of methyl iodide treatment in the latter case. In this type of reaction, part of the evidence for SN_2 displacement would

be covered up by the later treatment with methyl iodide.

The resemblance of the infra-red spectrum of the second peak from V. P. C. of runs R-5 and R-7 suggest that δ -valerolactone may have isomerized to γ -valerolactone (however, the boiling point of the later is lower than the former).

The resemblance of the infra-red spectrun of the first and second peak from V. P. C. of run R-10 suggests that the second peak may be butyl-δ-methoxyvalerate obtained by ester interchange of the methyl ester with butanol during the work up of the product.

Further work along these lines could be accelerated by obtaining δ-valerolactone by the depolymerization of a commercially available polymer(14). This would not only eliminate the dehydrogenation of 1,5-pentanediol, but also eliminate a time consuming separation. The yield of the methyl δ -methoxyvalerate could possibly be improved, by reacting the lactone and sodium methoxide at elevated temperature in the presence of the usual anhydrous diluent, toluene. An excess of sodium methoxide could also possibly increase the yield of methyl δ -sodoxyvalerate. The final reaction, involving the Williamson synthesis, could be improved by using an excess of methyl iodide instead of a stoichiometric amount. Since the boiling point of the methyl iodide is so low, the reaction might possibly be carried out using increased pressure. The use of a dry-ice condenser would enhance the reaction.

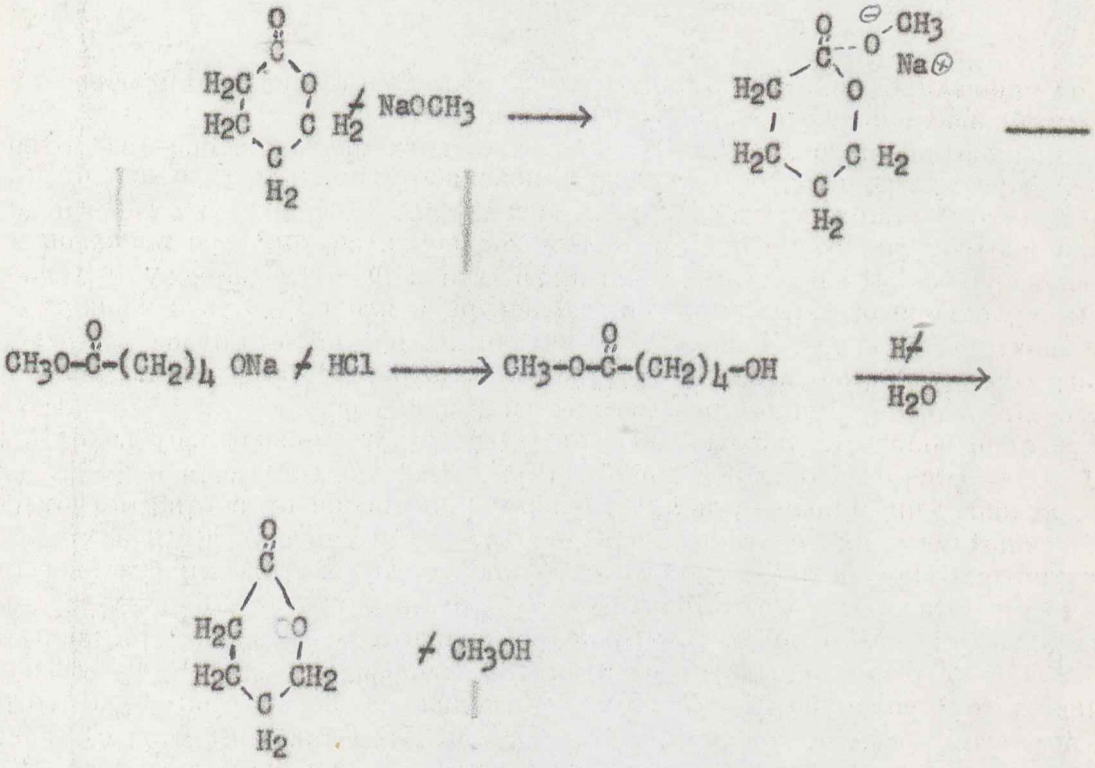
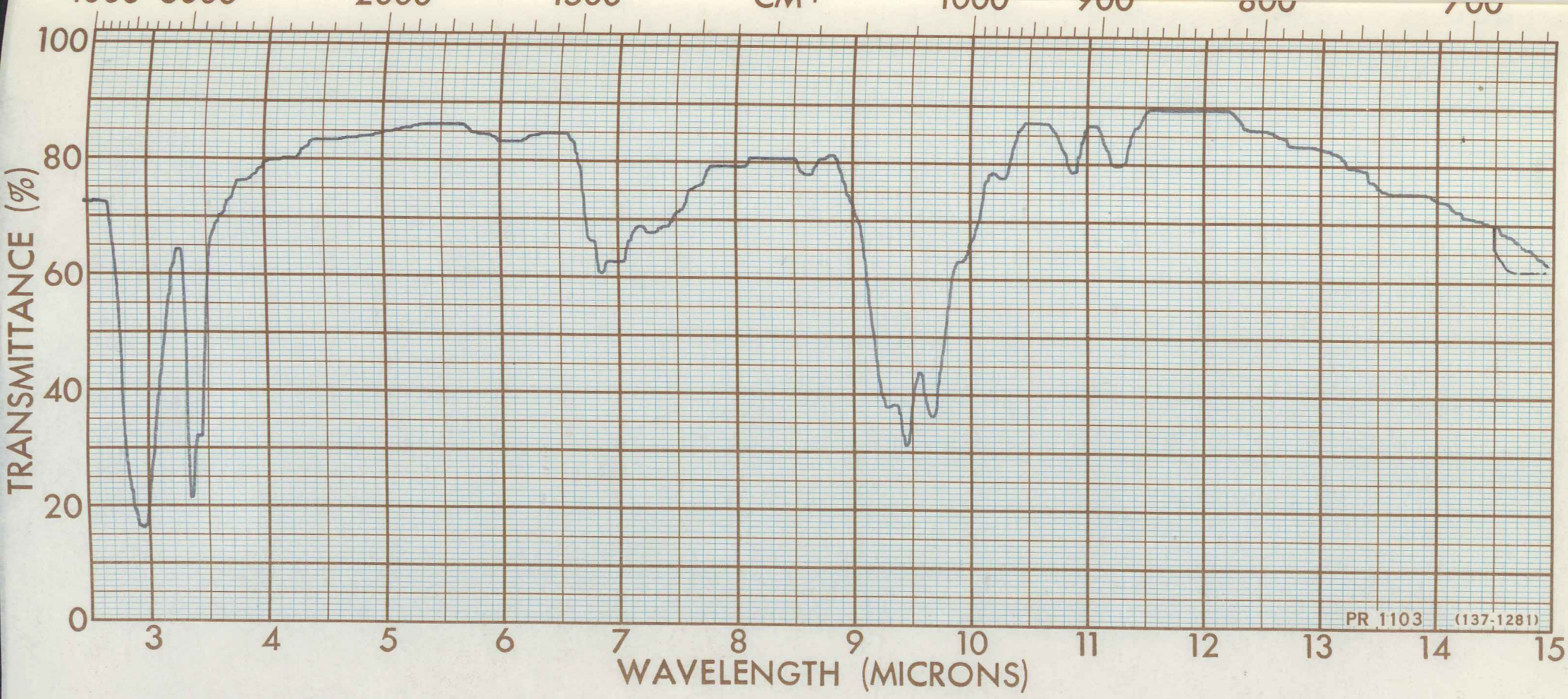


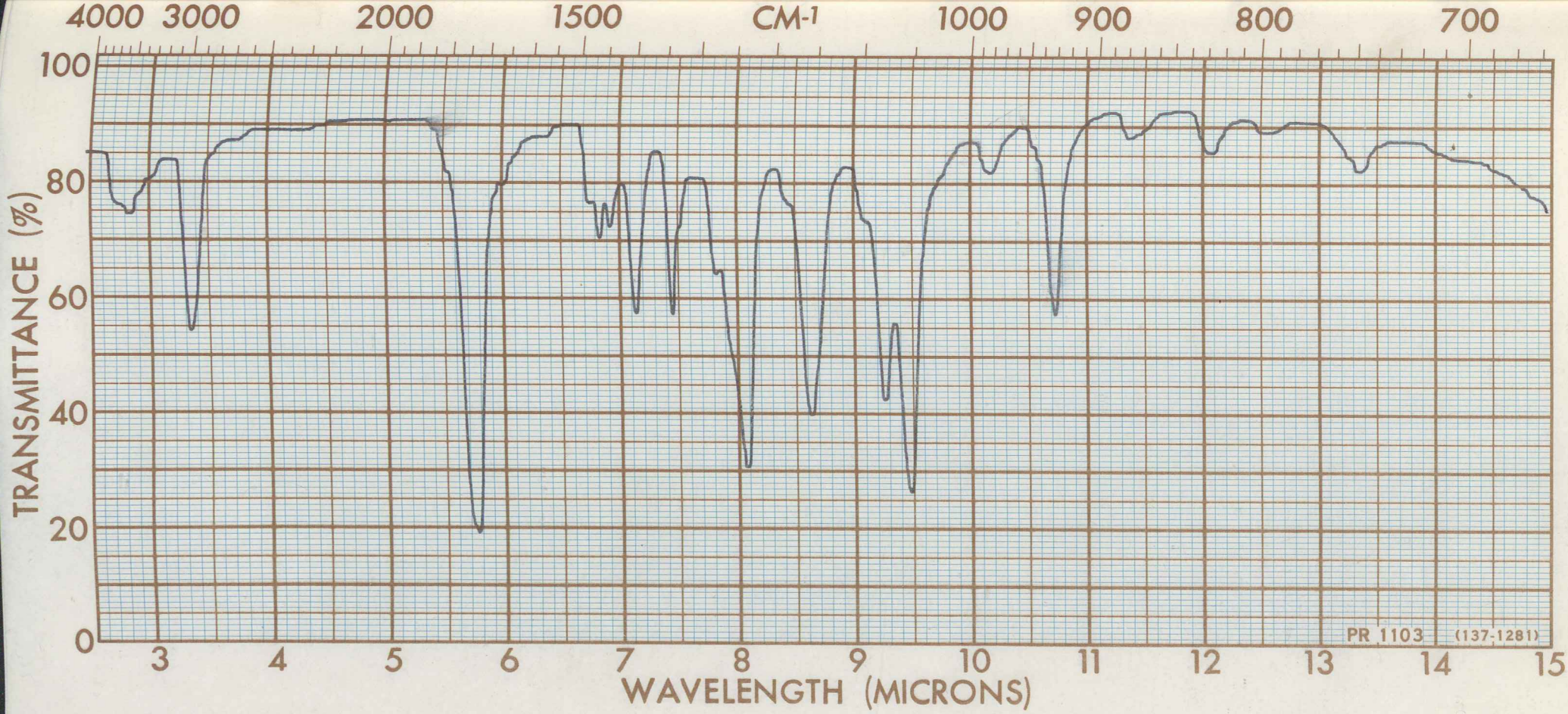
FIGURE 1



SPECTRUM NO._____	ORIGIN_____	LEGEND_____	REMARKS_____
SAMPLE_____	_____	1._____	_____
_____	PURITY_____	2._____	_____
_____	PHASE_____	DATE_____	_____
_____	THICKNESS_____	OPERATOR_____	_____

SPECTRUM NO. 1
SAMPLE 1,5-pentanediol

RECORDING CHARTS
GRAPHIC CONTROLS CORPORATION
BUFFALO, NEW YORK



SPECTRUM NO._____	ORIGIN_____	LEGEND_____	REMARKS_____
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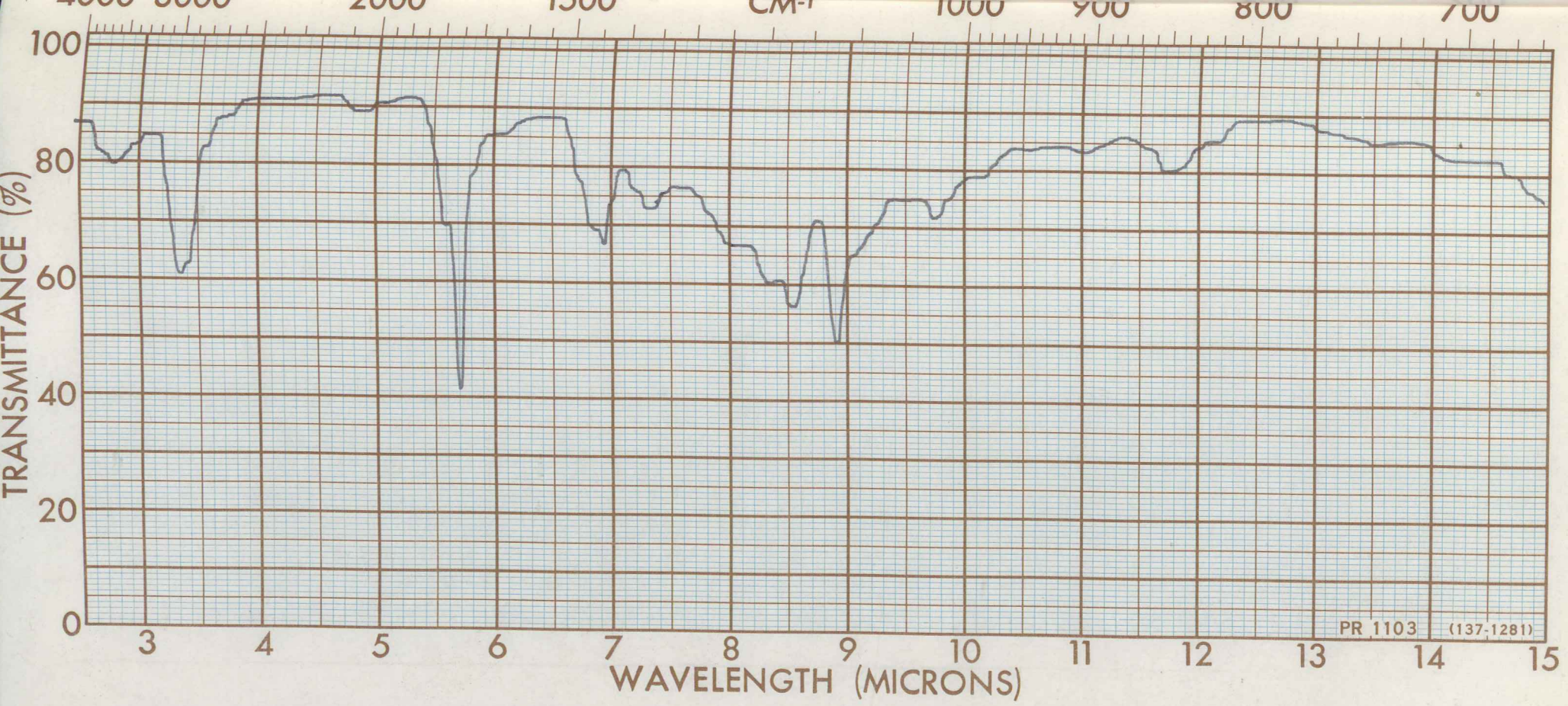
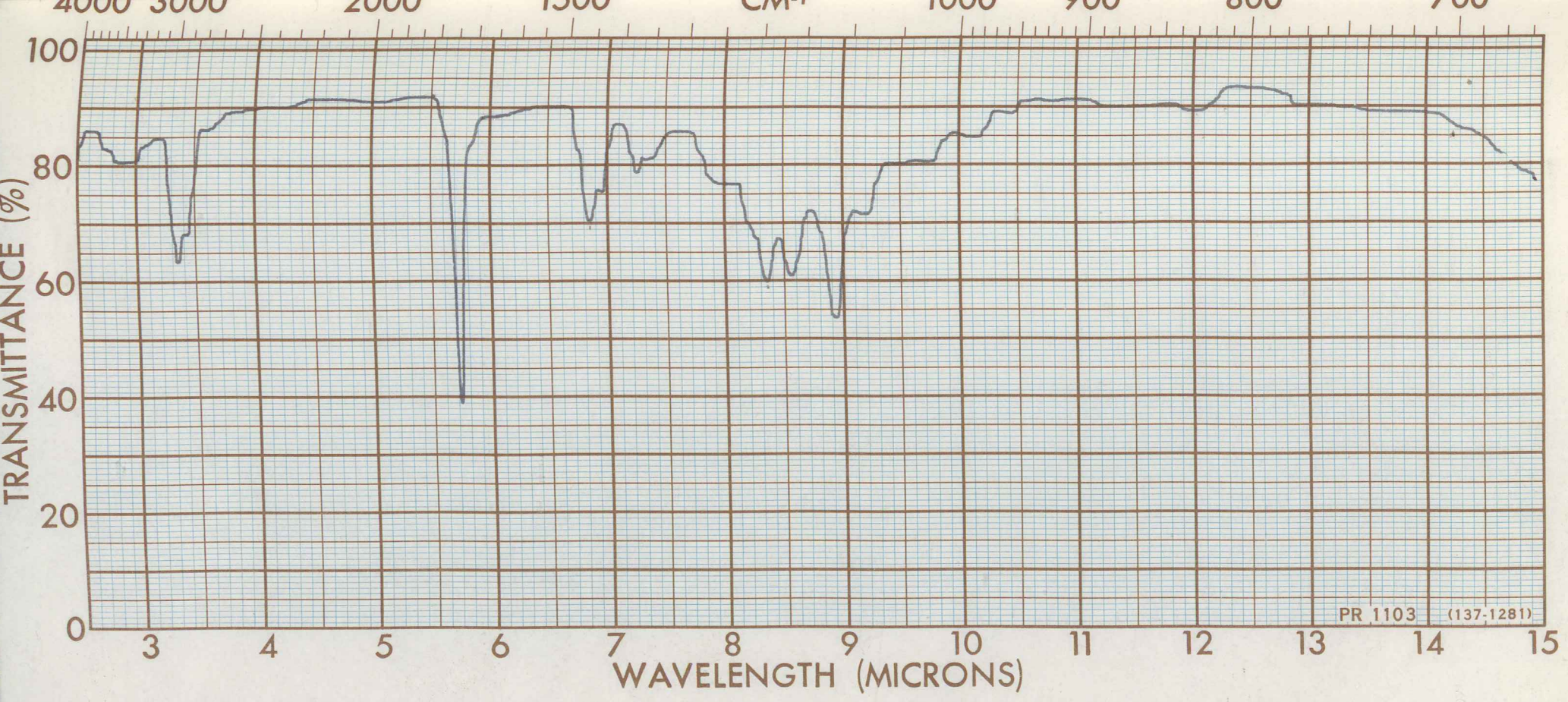
_____	PURITY_____	2._____	_____
_____	PHASE_____	DATE_____	_____
_____	THICKNESS_____	OPERATOR_____	_____

SPECTRUM NO. 2
SAMPLE δ-valerolactone



SPECTRUM NO._____	ORIGIN_____	LEGEND_____	REMARKS_____
SAMPLE_____	_____	1._____	_____
_____	PURITY_____	2._____	_____
_____	PHASE_____	DATE_____	_____
_____	THICKNESS_____	OPERATOR_____	_____

SPECTRUM NO. 3 20
SAMPLE Methyl δ-methoxyvalerat



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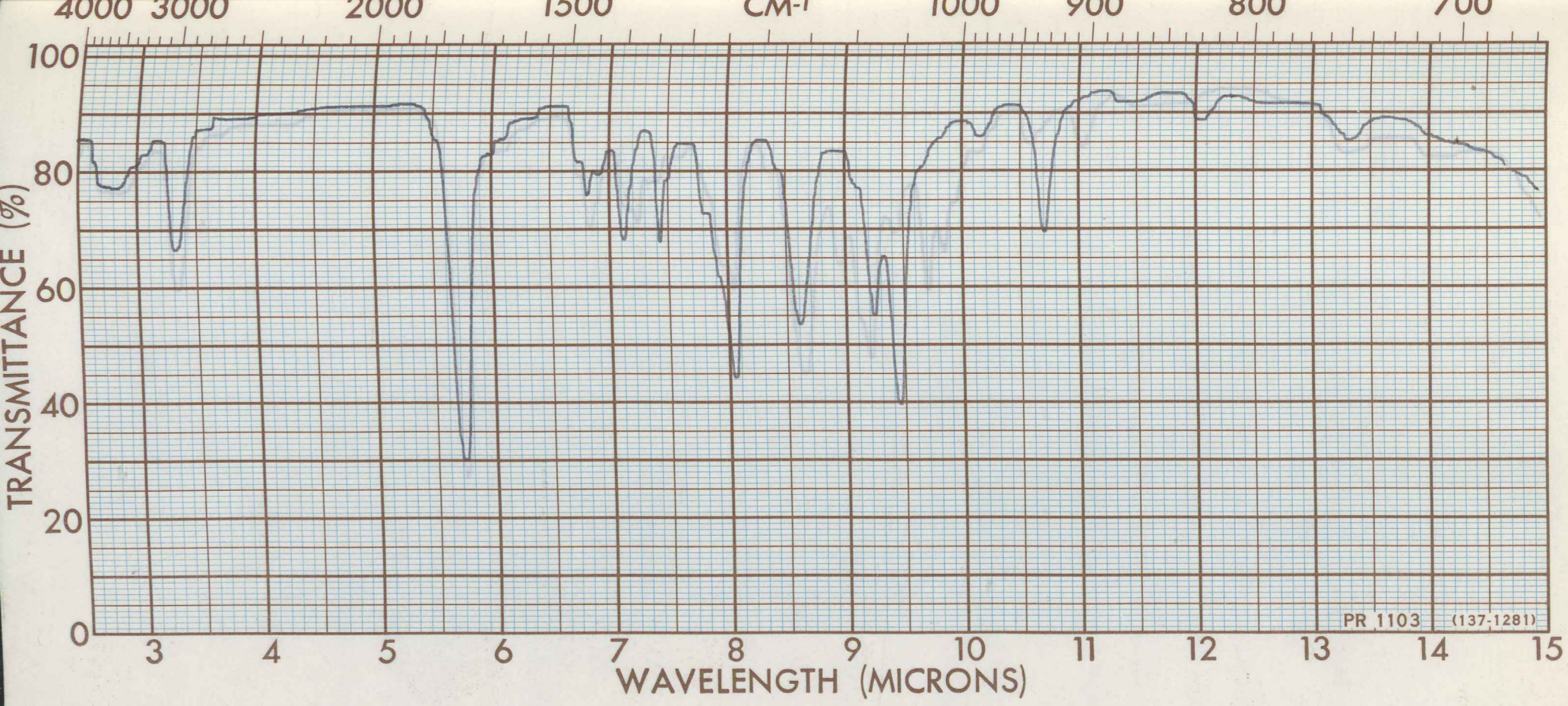
____	PURITY____	2.____	____
____	PHASE____	DATE____	____
____	THICKNESS____	OPERATOR____	____

SPECTRUM NO. 4
SAMPLE Butyl δ-methoxyvalerate

G RECORDING CHARTS
GRAPHIC CONTROLS CORPORATION
BUFFALO, NEW YORK



SPECTRUM NO._____	ORIGIN_____	LEGEND_____	REMARKS_____
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_____	THICKNESS_____	OPERATOR_____	_____

SPECTRUM NO. 5
SAMPLE δ-valerolactone

BIBLIOGRAPHY

(1) Zollinger, H., Azo and Diazo Chemistry, 87, Interscience Publishers, Inc., New York, (1961)

(2) Rose, A. K. and Yates, P., J. Am. Chem. Soc. 74 4703 (1952)

(3) Sheffer, H. E. and Moore, J. A., J. Org. Chem., 28 129, (1963)

(4) Hoster, D. P., Investigation into the Reactions of Aliphatic Methoxydiazoketones upon treatment with Boron Trifluoride Etherate, Dept. of Chemistry, Union College, (1963)

(5) Thielking, W. H., Synthesis and Reactions of Diazoketones, Dept. of Chemistry, Union College, (1963)

(6) Palomaa, S. and Kenetti, U., Berichte, 64 797 (1931)

(7) Leimu, R., Berichte, 70 1040-1053 (1937)

(8) Schniepp and Geller, J. Am. Chem. Soc. 69 1545 (1947)

(9) Bartlett, P. D. and Rylander, P. N., J. Am. Chem. Soc. 73 4273-74 (1951)

(10) Adkins, Burgoyne and Schneider, J. Am. Chem. Soc. 72 2626 (1950)

(11) Carothers, Dorough, Van Natta, J. Am. Chem. Soc. 54 761 (1932)

(12) Huntress and Mulliken, "Identification of Pure Organic Compounds," 197, John Wiley & Sons Inc., New York, (1941)

(13) Bellamy, L. J., The Infra-red Spectra of Comples Molecules 159, John Wiley & Sons, Inc., New York, (1954)

(14) Wheeler, O. H. and de Rodriquez, E. E. G., J. Org. Chem. 29 1227 (1964)